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Combining standard clinical blood values for improving survival prediction in patients with newly diagnosed brain metastases – development and validation of the LabBM-Score

Anna S. Berghoff (1,2), Fabian Wolpert (3), Tim Holland-Letz (4), Romina Koller (1,2), Georg Widhalm (2,5), Brigitte Gatterbauer (2,5), Karin Dieckmann (2,6), Peter Birner (2,7), Rupert Bartsch (1,2), Christoph C. Zielinski (1,2), Michael Weller (3), Matthias Preusser (1,2)

1 Department of Medicine I, Medical University of Vienna, Vienna, Austria

2 Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

3 Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland

4 Biostatistics Division, German Cancer Research Center, Heidelberg, Germany

5 Department of Neurosurgery, Medical University of Vienna, Vienna, Austria

6 Department of Radiotherapy, Medical University of Vienna, Vienna, Austria

7 Department of Pathology, Medical University of Vienna, Vienna, Austria

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CORRESPONDING AUTHOR:

Matthias Preusser, MD

Department of Medicine I and Comprehensive Cancer Center

Central Nervous System Tumours Unit (CCC-CNS)

Formatiert: Englisch (Vereinigte Staaten)

N-O-D-16-00595R2

Medical University of Vienna,

Waehringer Guertel 18-20,1090 Vienna, Austria

Tel: 0043 1 40400 44 45 0

Fax: 004 1 40400 44280

E-mail: matthias.preusser@meduniwien.ac.at

Formatiert: Englisch (Vereinigte Staaten)

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ABSTRACT

Background: We aimed to investigate the potential of standard hematologic and serum biochemical parameters to provide an independent and substantial contribution to the prediction of survival in patients with newly diagnosed brain metastases (BM).

Methods: Hemoglobin, white blood cell count (WBC), platelet count, serum albumin, creatinine, lactate dehydrogenase (LDH), and C-reactive protein (CRP) were assessed at diagnosis of BM in a discovery cohort of 1200 cancer. A multivariable Cox regression model was used to derive the LabBM Score. The LabBM Score score was externally validated in an independent cohort consisting of 366 patients.

Results: Hemoglobin below lower limit of normal (<LLN; HR 1.28; p=0.001), platelet count <LLN (HR 1.36; p=0.013), albumin <LLN (HR 1.19; p=0.038), LDH above upper limit of normal (>ULN; HR 1.51; p<0.001) and CRP >ULN (HR 1.52; p<0.001) were associated with survival in a multivariable Cox regression model and were included in the calculation of the LabBM score. Multivariable analysis including the LabBM Score and GPA class revealed an independent and significant association of the LabBM Score with OS (HR 1.42; 95% CI 1.29-1.57; p<0.001). The strong and independent association of LabBM score (HR 1.93; 95% CI 1.54-2.42) with OS prognosis was confirmed in the validation cohort.

Conclusion: Standard clinical blood parameters, combined in the easy-to-calculate LabBM Score, provide strong and independent prognostic information in patients with BM. The LabBM Score is an objective, inexpensive and reproducible tool to plan

clinical management strategies in BM patients and to improve patient selection and stratification for clinical trials.

Summary of importance: We introduce the easy-to-calculate LabBM Score, which is based on standard clinical blood parameters and provides strong and independent association with overall survival, irrespective of established prognostic factors in patients with newly diagnosed BM. The LabBM Score is an objective, inexpensive and reproducible tool to plan clinical management strategies in BM patients and to improve patient selection and stratification for clinical trials.

Keywords: brain metastases, laboratory parameters, hemoglobin, albumin, CRP, lactate dehydrogenase

INTRODUCTION

Brain metastases (BM) are a frequent complication occurring in up to 40% of cancer patients and are associated with high morbidity and mortality. Treatment modalities used for BM include neurosurgical resection, radiation therapy (radiosurgery and whole brain radiation therapy), chemotherapy, and increasingly also novel systemic drugs such monoclonal antibodies and tyrosine kinase inhibitors.[1, 2]

So far, BM are in general incurable and median overall survival times are in the range of few months.[3] However, survival times are highly variable with some patients succumbing to disease within few weeks and others achieving longer-term survival of several months or even years. Several BM-specific prognostic scores, such as the recursive partitioning assessment score (RPA), the graded prognostic assessment score (GPA) or the diagnosis-specific graded prognostic assessment score (DS-GPA), have been established to facilitate estimation of patient outcomes for clinical decision-making and use in clinical trials.[3] These scores are based on clinical characteristics such as patient age, Karnofsky performance status, status of the extracranial disease, number of BM and primary tumor type.[3] Although the use of BM-specific prognostic scores provides valuable information for patient management and has been widely adopted, especially in the context of clinical trials, the prediction of survival times is inaccurate and needs improvement.[4] Laboratory parameters routinely assessed in clinical practice have been shown to correlate with patient outcome in several diseases including cancer.[5-8] Therefore, we hypothesized that standard hematologic and serum biochemical parameters could be valuable for prediction of survival in BM patients. We tested and confirmed our hypothesis in a large and well-defined discovery cohort of 1200 patients treated for newly diagnosed

BM at the Medical University of Vienna and an independent validation cohort of 366 patients treated at the University Hospital Zurich. We provide an easy-to-calculate score based on standard clinical blood values that may be useful for survival prediction of BM patients in the clinical setting and in clinical trials (“LabBM Score”).

METHODS

Patients

The discovery cohort encompassed patients treated for newly diagnosed BM from solid extracranial cancers at the Medical University of Vienna between 1990 and 2013. The independent validation cohort included patients treated for newly diagnosed BM from solid extracranial cancers at the University Hospital Zurich between 2004 and 2014. The discovery and the validation cohort were treated by independent multidisciplinary teams according to good clinical practice guidelines.

Clinical data including information on the primary tumor, clinical course and survival times were retrieved by chart review. Graded prognostic assessment (GPA) was calculated according to previously published clinical characteristics.[3, 9] The ethics committee of the Medical University of Vienna (Vote 078/2004) and Zurich (Vote KEK-ZH-Nr. 2015-0559) approved the study.

Analyses of laboratory parameters

Hemoglobin level (g/dl), platelet count (G/l), white blood cell count (WBC; G/l), serum albumin (g/l), serum creatinine (mg/dl), serum lactate dehyrogenase (LDH; U/l) and serum C reactive protein (CRP; mg/dl) were analyzed as part of the routine clinical assessment in the local department of laboratory medicine. We retrieved for this study only blood values that were analyzed within 14 days before or after the diagnosis of BM. Local standard cut off parameters were used for definition of lower limit of normal (LLN), within normal range (NR) and upper limit of normal (ULN; **Supplemental table 1&2**).

Statistical Analysis

Overall survival (OS) was defined as time in months from diagnosis of BM to death or date of last follow-up. Primary tumor types with a frequency <5 were combined in the group “other primary tumor”. Laboratory parameters were classified into dummy variables (<LLN vs. NR vs. >ULN) according to the established local standard clinical cut off values (**Supplemental Table 1&2**). Then a univariable survival analysis was carried out for all parameters using Kaplan-Meier curves and two-sided log rank tests All laboratory parameters showing a statistically significant association ($p<0.05$) with survival prognosis in univariable analysis were included in the ~~multivariate~~ multivariable analysis.[10] Dummy variables were defined as <LLN vs. not <LLN and >ULN vs. not >ULN as appropriate for the specific laboratory parameter. Laboratory parameters with statistically significant association with survival in the multivariable model were included in the LabBM score. The regression coefficient B was used to calculate the LabBM score. In order to obtain an easy-to-use score, the regression coefficient B was multiplied by 2 and rounded, resulting in values between 0.5 and 1.0. Thus, 0 points were given for laboratory values within the normal range (NR) and depending on the parameter 0.5 to 1.0 points for values out of the normal range (LLN or ULN). The LabBM score was calculated for each patient in the discovery cohort. Based on the LabBM Score, 3 LabBM Score groups each containing one third of patients were defined in the discovery cohort, to give prognostic groups useful for clinical prognostic assessment and clinical trial planning. Patients with LabBM score 0-1 were defined to belong to the low LabBM score group, 1.5-2 to the medium LabBM score group and 2.5-3.5 to the high LabBM score group. Therefore, the higher the LabBM score group the more pathological laboratory parameters were present in the individual patient. For further statistically analysis the LabBM score groups (low, medium, high) were used.

Association of the LabBM score with survival was again analyzed in a univariable analysis (log rank test), as well as in a multivariable analysis (Cox regression model) including the LabBM Score in addition to the established clinical prognosis score GPA. The Harrell's C Index was calculated to investigate the prognostic accuracy of the LabBM Score.[11] Then the LabBM Score was calculated for the patients in the independent validation cohort and analyzed for association with survival. Again, association of the LabBM Score group was investigated in a univariable analysis (log rank test) as well as in a multivariable analysis (Cox regression model) including the LabBM Score group and the GPA class (entered as categorical variable) as the most frequently applied prognostic assessment.[9] To evaluate the added value of the LabBM Score groups Harrell's C index was calculated for both LabBM Score and GPA class. A two tailed p-value of < 0.05 was considered significant. The study was conducted according to the TRIPOD statement guidelines.[12]

RESULTS

Patients' characteristics

The discovery cohort consisted of 1200 patients and the validation cohort of 366 patients, all with newly diagnosed BM from a histologically proven extracranial solid cancer. **Table 1** lists further patients' characteristics including distribution of the investigated laboratory parameters. Due to the retrospective nature of this project, not all blood parameters were available in all patients. A complete set of all investigated laboratory parameter was available in 811/1200 (67.6%) patients in the discovery and 177/366 (48.4%) patients of the validation cohort. Albumin and LDH were most commonly missing, while all other parameters were available in the vast majority of cases (**Supplemental table 3**). No difference in survival according to the availability of complete set of all investigated laboratory parameters was observed in the discovery cohort (7 months vs. 6 months; p=0.355; log rank test). In the validation cohort, patients with missing laboratory parameters had better survival than patients with a complete set of all investigated parameters (13 months vs. 7 months; p=0.015; log rank test).

Prognostic impact of laboratory parameters in the discovery cohort

Hemoglobin (p<0.001; log rank test), platelet count (p<0.001; log rank test), WBC (p=0.005; log rank test), albumin (p<0.001; log rank test), creatinine (p=0.018; log rank test), LDH (p<0.001; log rank test) and CRP (p<0.001; log rank test) showed an association with survival on univariable analysis (**Table 2 Figure 1A-G**).

Development of the LabBM Score

All laboratory parameters were entered in a Cox regression model for multivariable analysis and score development. Here, hemoglobin <LLN (HR 1.280; p=0.001), platelet count <LLN (HR 1.365; p=0.013), albumin <LLN (HR 1.191; p=0.038), LDH >ULN (HR 1.515; p<0.001) and CRP >ULN (HR 1.525; p<0.001) showed an association with survival and were included in the further development of the LabBM Score. **Table 2** gives further details of the survival prognosis according to laboratory values in the discovery cohort. Next, the LabBM Score was formulated as indicated in the method section (**Table 3**). Based on the laboratory parameters, the LabBM score was calculated for 815/1200 (67.9%) patients in the discovery cohort, resulting in a score between 0 and 3.5 (**Table 4**). In 385/1200 (32.1%) patients calculation of the LabBM Score was not possible due to missing values (**Supplemental Table 3**). Importantly, Harrell's C index of the LabBM Score model was 0.6386 compared to 0.6465 if using all laboratory markers, showing that the information lost by the using the easy-to-use LabBM Score compared with the exact algorithm is minimal. In the discovery cohort survival of patients with missing LabBM Score did not differ from survival of patients with available LabBM Score (7 months vs. 7 months; p=0.266; log rank test).

Median LabBM score was 1 (range 0-3.5). 268/815 (32.9%) patients belonged to LabBM Score group 0-1, 299/815 (36.7%) to LabBM Score group 1.5-2, and 248/815 (30.4%) patients to LabBM Score group 2.5-3.5 (**Table 4**).

The LabBM score group showed a significant association with OS from diagnosis of BM in the discovery cohort. Patients with low LabBM Score group (0-1 points) had a median OS of 11 months, patients in the medium LabBM Score group (1.5-2 points) of 7 months and patients in high LabBM Score group (2.5-3.5 points) of 3 months

(p<0.001; log rank test; **Table 4; Figure 1H**). Accordingly, the LabBM Score group showed a HR 1.579 (95% CI 1.435-1.738; p<0.001; Cox regression model).

The GPA class presented with a statistical significant association with survival prognosis in the discovery cohort (HR 1.563; 95% CI 1.445-1.690; p<0.001; Cox regression model). To check whether the LabBM score contains information in addition to the GPA class, both variables were entered in a multivariable analysis. Here, the GPA class (HR 1.506; 95% CI 1.370-1.654; p<0.001: Cox regression model) as well as the LabBM Score group (HR 1.428; 95% CI 1.296-1.573; p<0.001; Cox regression model) showed an independent association with OS. The LabBM Score group presented with an independent statistical significant association with survival prognosis (HR 1.447; 95% CI 1.312- 1.597; p<0.001; Cox regression model) when entered with the individual data of the GPA i.e. age (HR 0.833; 95% CI 0.692- 1.002; p=0.053; Cox regression model), Karnofsky performance status (HR 0.404; 95% CI 0.326- 0.500; p<0.001; Cox regression model), number of BM (HR 0.623; 95% CI 0.518- 0.749; p<0.001; Cox regression model) and presence of extracranial metastases (HR 0.812; 95% CI 0.694- 0.951; p=0.010; Cox regression model). To address the added value of the LabBM Score compared to the existing and established GPA score Harrell's C index was calculated for both scores. Here, the GPA class showed a Harrell's C index of 0.619, indicating a gain of 24% in prognostic accuracy compared to a null model with Harrell's C index of 0.5. ~~and~~ ŧThe LabBM score group resulted in a Harrell's C index of 0.6386 and therefore the prognostic accuracy increased by 28% compared to the null model and by 4% compared to the model including only the GPA. Importantly, a combination score defined as the sum of GPA class and LabBM score showed a Harrell's C index of 0.680 and thereby an increase of prognostic accuracy by 36.1% compared to the null model, and by 12.1% compared to GPA only. (Supplemental table 5).

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~~, showing that both scores show an association with survival prediction and that the LabBM Score indeed increased predictive accuracy in comparison with GPA.~~

As the primary tumor type and applied BM therapy are additional important prognostic parameters, a multivariable analysis including the LabBM Score group, the GPA class, the primary tumor type and the applied therapy was calculated. As expected, the GPA class ($p<0.001$), the primary tumor type ($p<0.001$) as well as the applied therapy ($p<0.001$) showed associations with OS. In addition, also the LabBM Score group was significantly and independently associated with (HR 1.490; 95% 1.249-1.645; $p<0.001$; Cox regression model) OS.

Validation of the LabBM score

External validation was performed in an independent validation cohort, consisting of patients treated at the University Hospital Zurich. Calculation of the LabBM Score was possible in 199/366 (54.4%) patients, while 167/366 (45.6%) patients were excluded from the analysis due to missing laboratory parameters. Survival prognosis in patients with available laboratory parameters for LabBM Score calculation was inferior to patients with missing LabBM Score (7 months vs. 13 months; $p=0.010$; log rank test). The GPA class was statistically significantly associated with survival prognosis in the validation cohort (HR 1.477; 95% CI 1.228-1.777; $p<0.001$; Cox regression model).

Here, the LabBM Score groups confirmed the association with survival on univariable analysis. In the validation cohort, patients with low LabBM Score group (0-1 points) had a median OS of 10 months, patients in the medium LabBM Score group (1.5-2 points) of 6 months and patients in the high LabBM Score group (2.5-3.5 points) of 1

months ($p<0.001$; log rank test, **Table 4**; **Figure 1l**). In line with the results from the discovery cohort, the LabBM Score group had a HR of 1.985 (95% CI 1.588-2.483; $p<0.001$; Cox regression model). Again, the independent association of the LabBM Score group (HR 1.932; 95% CI 1.542-2.420; $p<0.001$; Cox regression model) was retained at the multivariable analysis including the GPA class (HR 1.249; 95% CI 0.978-1.595; $p=0.075$; Cox regression model).

DISCUSSION

BM are an increasing challenge in general oncology and their prevalence is likely to increase. The prognosis of BM is highly variable. Here we report that standard laboratory blood parameters, combined in the LabBM Score, have a robust and independent prognostic value in patients with newly diagnosed BM. We identified low hemoglobin levels, low platelet counts, low albumin levels, high LDH levels and high CRP as adverse prognostic factors. Importantly, all the parameters are routinely tested in cancer patients and display as surrogate parameters important information on the bone marrow reserve, liver function, tumor cell turnover and infection. Several of these parameters have previously been reported as prognostically relevant in patients with advanced cancer and also non-malignant disorders.[5, 7, 8, 13-16] The causes of laboratory anomalies may be manifold in cancer patients and may include previous applied therapies, paraneoplastic factors, effects of chronic disease, bleedings, malnutrition, toxicities of prior or concurrent therapies and others. Low hemoglobin and platelet counts may be surrogate parameters of impaired bone marrow reserve, low albumin levels may indicate malnutrition, and high LDH and CRP levels may be associated with high tumor load or underlying infections.[15, 17] We did not intend to analyze the specific cause of abnormal blood values in individual cases, but view the LabBM score rather as a general indicator of disease activity and the patient´s biological constitution at the time of BM diagnosis. Of note, we investigated in our study only blood parameters measured at diagnosis of brain metastases and not during the disease course. Future research may evaluate the prognostic impact of blood values changes over time.

We consider the LabBM score as easy to apply in clinical practice, because it is based on routinely investigated parameters. In addition, the LabBM score is based on objectively measurable parameters, as blood values are in general assessed in specialized, certified and quality controlled laboratories and according to strict standard operating procedures. Other prognostic scores used for BM patients are based on more subjective criteria. The physician-assessed clinical performance score (e.g. KPS), which is prone to some inter-observer variability, is a core parameter of the GPA.[18] Importantly, the prognostic value of the LabBM score was independent of the established prognostic GPA score as well as the histological tumor type and the applied therapy, thus indicating that consideration of blood values in addition to clinical parameters has added value for estimation of survival probabilities in BM patients.

Despite the large investigated patient cohort of overall 1566 patients, the opportunity to investigate two separate cohorts and the availability of high-quality and detailed clinical data, our study has limitations. Due to the retrospective nature of this project, not all blood parameters were available in all patients. A complete set of all laboratory parameters of interest was available in 811/1200 (67.6%) patients in the discovery and 177/366 (48.4%) patients of the validation cohort. Albumin and LDH were missing in 28% and 17% of patients, respectively, while all other parameters were available in the vast majority of cases. Patients with missing values had a longer survival compared to patients with the full set of investigated laboratory parameters in the validation cohort. Although this finding might be a chance association, it might also be hypothesized that patients in a general good health status might be less likely to receive a full set of laboratory investigation compared to patients in an impaired health status. However, we decided to include all available

patients in the calculation and validation of the LabBM score to exclude any kind of inclusion bias. For optimal application of the LabBM score in the clinical setting standardized measurement of all five relevant parameters should be ensured. The two investigated cohorts were treated at two different centers and therefore resemble the standard real life cohorts at these particular centers. Although, the cohorts differ in some clinical characteristics the LabBM Score resulted in comparable results in both cohorts as an independent association with estimated survival was shown in both cohorts. Therefore, these data suggest that although our cohorts presented with some clinical differences, the LabBM Score is applicable to real life cohorts across centers. Although the large sample size and the utilization of two cohort provide large statistical power and external validation of our results, the retrospective nature of our data need to be acknowledged as limitation and make prospective validation of the LabBM score desirable.

In conclusion, the LabBM Score provides an objective, inexpensive and easily reproducible tool to estimate survival of patients with newly diagnosed BM. The LabBM score has an independent association with overall survival prognosis, irrespective of other established prognostic factors like the GPA class and adds substantial prognostic accuracy. In the future, the LabBM Score may help to plan clinical management strategies in BM patients or to improve patient selection and stratification for clinical trials.

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Figure legend

Figure 1: Overall survival according to laboratory parameter in the discovery cohort: **A** Hemoglobin; **B** Platelet count; **C** White blood cell count (WBC); **D** Albumin; **E** Creatinine; **F** Lactate dehydrogenase (LDH); **G** C reactive protein (CRP); Survival according to LabBM Score group in the discovery cohort (**H**) and the validation cohort (**I**); Abbreviations: LLN: Lower Limit of Normal; ULN: Upper Limit of Normal; NR: Normal range

Dear Editor,

We would like to thank you and the reviewers for your efforts and the constructive feedback that certainly helped us to significantly improve our manuscript. We have carefully addressed all issues and suggestions. Please find below our point-to-point response to the reviewers' comments:

Reviewer #1

Berghoff and colleagues have addressed most of my comments appropriately. However, the main issue of this paper, whether the LabBM score is of (substantial) additional value in predicting survival, remains unclear to me. My question was if the LabBM score provided additional prognostic accuracy in addition to the established prognostic factors, for example calculated with Harell's C-index. Although the authors have calculated these C-indices 'for both scores', it is unclear to me how these models exactly look like. Which variables are included and what does this outcome tells us? Supplementary table 4 does not provide this answer.

What I would like to see is results of:
1) A model with no variables (a null model)
2) A model with the clinical variables only
3) A model with the clinical variables and the LabBM score
For example, if the prognostic accuracy increases from 0.5 (the null model) to 0.619 (model 2, with clinical variables only), this represents a gain of 24% ((0.619-0.5)/0.5). If model 3 has a value of 0.6386, the gain is 28% ((0.6386-0.5)/0.5). This would mean that the additional prognostic value of the LabBM score is only 4%.

If the analysis was indeed performed as stated above, I doubt if the LabBM score is indeed of substantial additional value. Although the LabBM is a strong and independent prognostic factor for survival, the increase in prognostic accuracy is only 4% when compared to the clinical variables alone.

Could the authors explain how they conducted the analysis and if they feel that the additional prognostic accuracy is indeed substantial?

Our response: In order to address the reviewers question we added the following paragraph to the results section:

"…To address the added value of the LabBM Score compared to the existing and established GPA score Harrell's C index was calculated for both scores. Here, the GPA class showed a Harrell's C index of 0.619, indicating a gain of 24% in prognostic accuracy compared to a null model with Harrell's C index of 0.5. The LabBM score group resulted in a Harrell's C index of 0.6386 and therefore the prognostic accuracy increased by 28% compared to the null model and by 4% compared to the model including only the GPA. Importantly, a combination score defined as the sum of GPA class and LabBM score showed a Harrell's C index of 0.680 and thereby an increase of prognostic accuracy by 36.1% compared to the null model, and by 12.1% compared to GPA only. (Supplemental table 5)…"

Therefore, the LabBM sore adds substantial prognostic accuracy as the addition of the LabBM score increases the prognostic accuracy from 24% for GPA alone to

36.1% for the combination. We induced this information in the discussion section:

"…The LabBM score has an independent association with overall survival prognosis, irrespective of other established prognostic factors like the GPA class and adds substantial prognostic accuracy…"

Further we included supplemental table 5 including the results of all Harrell's C models.

Included variables	Harrell's C index	Increase in prognostic accuracy compared to null model
No variables	0.5	-
GPA	0.619	24%
LabBM score	0.639	28%
GPA + LabBM score	0.683	36.6%

Minor comment:
1) 'Multivariate' is not everywhere changed into 'multivariable' (page 8 statistical analysis, supplementary table 4).

Our response: As suggested by the reviewer 'multivariate' was changed to 'multivariable' in the indicated sections.

Reviewer #2: Critiques have been addressed
Reviewer #3: Thank you for your review. Nothing to add.

Our response: We thank reviewer #2 and reviewer #3 for the approval of our work.

Sincerely,

Anna Berghoff, Tim Holland-Letz and Matthias Preusser, on behalf of all co-authors

SUPPLEMENTAL TABLES

Supplemental Table 1: Standard values of laboratory parameters in the discovery cohort

Parameter	Lower limit of normal (LLN)	Normal range (NR)	Upper limit of normal (ULN)
Hemoglobin (g/dl)			
male	≤13.4	13.5-18.0	≥18.1
female	≤11.9	12.0-16.0	≥16.1
Platelet count (G/l)	≤149	150-350	≥351
WBC (G/L)	≤3.9	4.0-10.0	≥10.1
Albumin (g/l)	≤34.9	≥35	-
Creatinine (mg/dl)			
male	≤0.6	0.7-1.2	≥1.3
female	≤0.4	0.5-0.9	≥1.0
Lactat dehydrogenase (LDH; U/L)	-	≤249	≥250
C-reactive protein (CRP; mg/dl)	-	≤0.50	≥0.51

Supplemental Table 2: Standard values of laboratory parameters in the validation

Parameter	Lower limit of normal (LLN)	Normal range (NR)	Upper limit of normal (ULN)
Hemoglobin (g/dl)			
male	≤13.4	13.5-17.0	≥17.1
female	≤11.6	11.7-15.3	≥15.4
Platelet count (G/l)	≤141	142-400	≥401
WBC (G/L)	≤2.9	3.0-9.6	≥9.7
Albumin (g/l)	≤39	≥40	-
Creatinine (mg/dl)			
male	≤0.61	0.62-1.06	≥1.07
female	≤0.43	0.44-0.8	≥0.9
Lactat dehydrogenase (LDH; U/L)	≤239	240-480	≥481
C-reactive protein (CRP; mg/dl)	-	≤0.50	≥0.51

Supplemental Table 3: Available and missing laboratory parameters in the discovery and validation cohort

Laboratory parameter	**Discovery cohort (n=1200)**		**Validation cohort (m=366)**	
	n	%	n	%
Hemoglobin				
Available	1200	100	366	100
Missing	0	0	0	0
Platelet count				
Available	1200	100	366	100
Missing	0	0	0	0
WBC				
Available	1200	100	363	99.2
Missing	0	0	3	0.8
Albumin				
Available	874	72.8	258	70.5
Missing	326	27.2	108	29.5
Creatinine				
Available	1164	97.0	329	89.9
Missing	36	3.0	37	10.1
LDH				
Available	1032	86.0	269	73.5
Missing	168	14.0	97	26.5
CRP				
Available	1112	92.7	367	100
Missing	88	7.3	0	0

Abbreviations: WBC: White blood cell count; LDH: lactate dehydrogenase; CRP: C reactive protein

Supplemental Table 4: Results of the multivariable analysis in the validation cohort

	Multivariable analysis (Cox regression model)		
	HR	**95% CI**	**P-value**
LabBM Score Group			
Low (0-1 point) (categorical)			<0.001
Medium (1.5-2 points)	0.441	0.363-0.534	<0.001
High (2.5-3.5 points)	0.538	0.448-0.646	<0.001
GPA Class			
Class I (categorical)			<0.001
Class II	0.365	0.264-0.505	<0.001
Class III	0.415	0.312-0.551	<0.001
Class IV	0.685	0.560-0.838	<0.001
Primary tumor type			
Lung cancer (categorical)			
Breast cancer	1.257	0.872-1.812	0.221
Melanoma	1.180	0.810-1.718	0.389
Renal cell carcinoma	1.771	1.182-2.655	0.006
Colorectal cancer	0.888	0.583-1.352	0.579
Cancer of unknown primary	1.411	0.925-2.152	0.110
Others	1.928	1.009-3.686	0.047
Treatment			<0.001
Stereotactic Surgery (categorical)			
Chemotherapy	0.233	0.136-0.399	<0.001
Surgery	0.199	0.071-0.556	0.002
Whole brain radiation therapy	0.252	0.148-0.431	<0.001
Best supportive care	0.330	0.192-0.570	<0.001

Supplemental Table 5: Results of all Harrell's C models

Included variables	Harrell's C index	Increase in prognostic accuracy compared to null model
No variables	0.5	-
GPA	0.619	24%
LabBM score	0.639	28%
GPA + LabBM score	0.680	36.1%